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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,538	05/02/2002	Audrey Goddard	P3230R1C001-168	1052

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EXAMINER	
SEHARASEYON, JEGATHEESAN	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,538	GODDARD ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon, Ph.D	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is in response to Applicants response filed 11/23/2005. Claim 1-3 remain cancelled. Therefore claims 4-17 are pending and the subject of this action.

2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

3. The Office acknowledges the submission of the IDS dated 11/23/2005.

Priority

4. Applicants arguments with respect to the priority has been considered but it is not found to be persuasive. Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 as indicated in the previous Office Actions of 3/31/2005 and 8/29/2005. Applicants have argued that they are entitled to the benefit of the filing date of at least August 24, 2000 based on the disclosure in the PCT Application PCT/US00/23328 filed 8/24/2000 of the differential tissue expression distribution in tumor versus normal tissue (example 18). Although, the previous patent application discloses the same polypeptide (SED ID NO: 34) sequence and polynucleotides (SEQ ID NO: 33) encoding the polypeptide as the instant specification, the disclosure is not enabling for the instant invention and because the disclosed function does not impart utility to the instant invention for the reasons set forth below and the previous Office Action. Therefore, the filing date of 2 May 2002 is maintained as the priority date.

35 U.S.C. § 101/112, first paragraph, Lack of Utility, Enablement, maintained

5. Claims 4-17 remain rejected under 35 U.S.C. 101, as lacking utility is maintained and under 35 U.S.C. 112, first paragraph for reasons set forth in the previous Office Actions recited in pages 4-8 of 28, June 2004, pages 3-17 of 31, March 2005 and pages 3-14 of 29 August 2005. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth in the previous Office Actions recited in pages 4-8 of 28, June 2004, pages 3-17 of 31, March 2005 and pages 3-14 of 28, June 2005, one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue that the utilities of PRO1277 polypeptide include the use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1277 cDNA is more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor. Applicants have also extensively discussed the utility guidelines (pages 3-6). Applicant's arguments (23 November 2005) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing that polynucleotide sequence of SEQ ID NO: 27 (DNA56869-1545) is more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts. In addition, blast search provided asserts that PRO1277 is a secreted transmembrane polypeptide. There is no further supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is also differentially expressed in the normal tissue compared to the tumor tissue and as such one of skill in

the art would conclude that it is not supported by a substantial asserted utility or a well-established utility. Contrary to Applicants assertion that PRO1277 polypeptide is differentially expressed (23 Novewmber 2005, pages 14-16), Applicants only demonstrate more highly expressed cDNA for PRO1277 in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts. The argument presented evinces that instant specification provides a mere invitation to experiment, and not readily available utility. There is no description in the specification to that would indicate a correlation with higher expression levels of the message to the PRO1277 polypeptide. It remains that; there is no information on the record as to whether the claimed protein is expressed at all in the skin tissue and esophageal tissue cancerous or otherwise.

Given the increase in message (cDNA) for PRO1277 in the expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a more highly expressed mRNA would directly correlate with increased polypeptide levels. Although, Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase (see page 10), the evidence of record does not support this assertion. Further research needs to be done to determine whether the increase of PRO1277 cDNA in expression in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts supports a role for the polypeptide

in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
>
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Applicant's assertions that the claimed PRO1277 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics do not provide a substantial utility for the claimed protein.

Haynes et al (1998, Electrophoresis, 19: 1862-1871), Hu et al. (2003, Journal of Proteome Research 2: 405-412) and Chen et al. (2002, Molecular and Cellular Proteomics 1: 304-313) were discussed previously in the Office Action dated 20 August 2005. Gygi et al. (1999, PTO1449 of 7/01/05) determined the correlation between mRNA and protein expression levels for selected genes expressed in yeast. It was found that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data (abstract).

Contrary to Applicants assertion that Haynes et al. does not contradict the utility and enablement of the instant claims (page 19 of the response), Haynes et al. states that "These results suggest that even for a population of genes predicted to be relatively homogeneous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA" (page 1863, 2nd paragraph). Although, Applicants assert that there is a strong correlation between mRNA expression and protein expression, Gygi et al. conclude that transcript levels provide little predictive value with respect to the extent of the protein expression (page 1730, last line). Applicants contend that Haynes and Gygi et al. have absolutely no bearing on the instant invention because they looked at the static level of mRNA across many genes not changes in the level of expression for single gene. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., changes in message levels are correlated to protein levels) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). While it is true that Haynes and Gygi references discussed the steady state levels, they were relied upon by the Office to illustrate the point that in general there is no correlation between mRNA expression and the polypeptide expression. In addition, Applicants have failed to establish that there exists a correlation between the message levels and the protein levels of PRO1277 either in steady state or in a dynamic changing environment.

Contrary to Applicants assertion that Hu et al.'s methodology provides little or no information regarding biological significance of genes with less than 5-fold expression change in disease, the reference teaches that "careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level change".

The declarations of Mr. Grimaldi and Dr. Polakis filed under 37 CFR 1.132 were previously considered in the Office Action dated 31 March 2005 and 29 August 2005. The declarations are found to be insufficient to overcome the rejection of pending claims 4-17, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the Office Action dated 31 March 2005 and 29 August 2005. Applicants' arguments have been fully considered but are found to be persuasive as discussed extensively on pages 8-11 of the Office Action dated 29 August 2005.

The specification describes only mRNA expression data. The argument presented evinces that instant specification provides a mere invitation to experiment, and not readily available utility. Furthermore, as indicated above the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see Hu et al discussions above). It is also not known whether PRO1277 polypeptide is expressed in skin and esophagus tissue. There is no nexus between the mRNA expression and PRO1277 polypeptide expression (No nexus between changes mRNA levels and changes in polypeptide level). In the absence of any of the above information, all that the specification does is present evidence that the mRNA encoding PRO1277 is present at

higher levels in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts, and invite the artisan to determine the rest of the story. This is further borne out by Grimaldi assertion that "additional studies can then be conducted if further information is desired" (Appendix A, paragraph 7). Such is insufficient to meet the requirements of 35 U.S.C. § 101 utility for the claimed polypeptides.

Although, Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide, it is important to note that the instant specification provides no information regarding protein levels. Only mRNA expression data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 4-17 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels. Furthermore, the declarations do not provide data such that the examiner can independently draw conclusions. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, as discussed above in Hu et al. In addition, as discussed above Haynes et al., Chen et al. and Gygi et al. disclose that the correlation between mRNA expression and protein expression is poor at best.

In the declaration filed under 37 CFR 1.132, senior research associate Mr. Grimaldi has asserted that, if a difference in mRNA is detected, this indicates that the gene and its corresponding polypeptide are useful for diagnostic purposes, to screen

samples to differentiate between normal and tumor tissues. It is further stated that additional studies can then be conducted if further information is desired, which Applicants find is taken out of context. In paragraph 7, declarant indicates that the difference (changes) in the expression is expected to be reflected in the difference (changes) in the corresponding protein. However, there is no description in the specification to that would indicate a correlation with higher or lower expression levels of the message to the PRO1277 polypeptide. Applicants further citing the second Grimaldi declaration (Exhibit 2) filed under 37 CFR § 1.132 argues that, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed..... this same principal applies to gene under-expression." Citing paragraph 5, Applicants contend that "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for the diagnosis and treatment."

At paragraph 4 of the second Grimaldi declaration (Exhibit 2), the declarant discusses mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant

specification provides a mere invitation to experiment, and not a readily available utility. The PRO1277 gene, unlike the well known Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t (5;14), no translocation of PRO1277 gene is known to occur. All that the specification demonstrates is that the PRO1277 nucleic acid (mRNA) was more highly expressed in expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts. No mutation or translocation of PRO1277 gene has been associated with for example, skin and esophageal tumor. Therefore, in the absence of any of the above information, all that the specification does is present evidence that the mRNA encoding PRO1277 is more highly expressed in an unknown number of samples, and invite the artisan to determine the rest of the story. Such is insufficient to meet the requirements of 35 U.S.C. § 101 for the claimed PRO1277 polypeptide.

The specification describes only mRNA expression data. The argument presented evinces that instant specification provides a mere invitation to experiment, and not readily available utility. Furthermore, as indicated above the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see Hu et al discussions above). It is also not known whether PRO1277 polypeptide is expressed in normal skin or normal esophageal tissues. There is no nexus between the changes in mRNA expression and changes in PRO1277 polypeptide. In the absence of any of the above information, all that the specification does is present evidence that the mRNA encoding

PRO1277 is present at higher levels in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts, and invite the artisan to determine the rest of the story. This is further borne out by Grimaldi assertion that "additional studies can then be conducted if further information is desired" (Appendix A, paragraph 7). Such is insufficient to meet the requirements of 35 U.S.C. § 101 utility for the claimed polypeptides.

The Polakis declaration states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr Polakis characterizes the instances where such a correlation does not exist as exceptions to the rule. Although, Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide, it is important to note that the instant specification provides no information regarding protein levels. Only mRNA expression data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 4-17 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels. Furthermore, the declarations do not provide data such that the examiner can independently draw conclusions. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, as discussed above in Hu et al. In addition, as discussed above Haynes et al., Chen et al. and Gygi et al.

disclose that the correlation between mRNA expression and protein expression is poor at best.

Applicants along with Mr. Grimaldi, and Dr. Polakis declarations, also provide teachings from Molecular Biology of the Cell by Bruce Alberts and Genes VI (1997) by Ben Lewin, to support their assertion that there is a correlation between increased gene expression and increased protein expression (page: 20 and 21). Applicants also refer to additional articles by Zhigang et al., and Meric et al. as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Zhigang et al. describe a specific example of the expression of prostrate stem cell antigen (PSCA) protein and mRNA to validate it as potential molecular target for diagnosis and treatment of human prostrate cancer. It is asserted that the data shows " a high degree of correlation between PSCA protein and mRNA expression". Further Meric et al. states "the fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. Meric et al. also teaches that most efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Although, Applicants contends that the regulation is primarily at the transcriptional level, the prior art evidence discussed above teach that gene expression is quite complicated, however, and is also regulated at the level of mRNA transcription, mRNA stability, mRNA translation and protein stability. Further reading of Meric et al. casts doubts on Applicants claim that there is a direct correlation between increased mRNA levels and the level of expression of the encoded protein. For

example, the reference discusses that variations in mRNA sequences increase or decrease translational efficiency as found in BRCA1 (see pages 973-974). In addition, advances in technology allowing comparisons of message and protein using proteomics show a lack of correlation as evidenced by Haynes et al., Chen et al., and Gygi et al.

Applicants claim regardless of the cause of the differential expression, the fact that there is a higher level of expression PRO1277 of gene in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts allows this mRNA expression to be used as a diagnostic tool. These arguments have been fully considered but are found to be persuasive because the of the lack of information on the record whether the claimed protein (PRO1277) is expressed at all in skin and esophageal tissue, cancerous or otherwise would make significant further research a necessity.

Applicants assert that they have established that the accepted understanding in the art is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein. Haynes et al. and Chen et al. teachings listed above and discussed contradict Applicants assertion that there exists a direct correlation between mRNA levels and the level of expression of the encoded protein. In fact, the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissues. Therefore, there is no evidence to support Applicants' assertion that there is working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels. Contrary to Applicants assertions the declarations and cited references

do not establish a substantial utility for the claimed PRO1277 polypeptide molecules. As stated above, the specification does not provide sufficient guidance to the skilled artisan to diagnose or treat any disease. Although, Applicants argue that the Office has not offered any arguments or cited any reference to establish "that one of ordinary skill in the art would reasonably doubt" that a polypeptide differentially expressed in certain tumors ca be used as a diagnostic tool, the specification only demonstrates differential mRNA expression without a nexus to polypeptide expression.

A utility such as cancer research would in fact be specific to the polypeptide. However, further research is required to ascertain whether the protein levels of PRO1277 are altered and thus provide a substantial, that is, real-world and reasonable confirmed, utility. Since the peptide of SEQ ID NO: 34 does not posses a specific, substantial or well-established utility, the chimeric proteins comprising this polypeptide also lacks utility. Although, Applicants contend that the PTO has failed to offer any arguments or cite any references to establish "that one of ordinary skill in the art would reasonably doubt" that a polypeptide differentially expressed in certain tumors can be used as a diagnostic tool, hey do not offer any evidence for such. Therefore, for all of these reasons, the rejection of claims 4-17 based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office Action is maintained.

35 USC § 112, first paragraph – Enablement, maintained

6. Claims 4-5 and 12-17 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one of skilled in the art to which it pertains, or with

which it is most closely connected, to make and/or use the invention commensurate in scope with these claims is maintained for reasons set forth in the previous Office Actions (28 June 2004, 31 March 2005 and 29 August 2005). Even if the specification taught how to use the PRO1277 polypeptide (SED ID NO: 34), enablement would not be commensurate in scope with claims 4-5, and 12-17, which encompass % variants of SED ID NO: 34 (claims 4-5, for example), and various fragments of SED ID NO: 28 (claims 4-5, 14 and 15 for example).

Applicants are not enabled for polypeptides that have at least 95-99% identity to SED ID NO: 34 or the various fragments of SED ID NO: 34 because there is no structural or functional information provided in the specification.

Applicants submit that the claimed polypeptides are enabled, as one of skilled in the art would know how to make and use them. They also contend that it is well-established in the art how to make and use them. These arguments have been previously addressed on pages 14-15 of the Office Action dated 29/8 /05. Applicants' arguments have been fully considered but are not found to be persuasive. Even if one of skilled in the art was able to generate polypeptides that are 95% or 99% identical to SEQ ID NO: 34, will require undue experimentation to assign the functional limitations to these polypeptides. Although, Applicants have previously amended the claims to assert that the said polypeptide is highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed normal esophageal tissue or normal skin compared to esophageal tumor or melanoma

tumor counterparts or fragments thereof used to generate an antibody that specifically binds SEQ ID NO: 34, there is no way of knowing which, if any, variants or fragments would have the same property of higher expression in the specific tissue. There is no nexus between the degree of homology and regulation of gene expression. Until one identifies a particular variant that demonstrates a higher expression or not, one of skilled in the art would not know the expression profile of the variant. Modifications to the protein, e.g., by substitutions or deletions, would often result in deleterious effects to overall activity and effectiveness of the protein.

Accordingly, the disclosure fails to enable such a myriad of the claimed polypeptide molecules that not only vary substantially in length, but also in polypeptide composition and to provide any guidance to one skilled in the art on how to make and use the claimed genus of polypeptide molecules. Thus, it would require undue experimentation for one skilled in the art to make and use the claimed genus of the molecules embraced by the instant claims. Therefore, the rejection of record is maintained.

In addition, the lack of direction/guidance presented in the specification regarding which variants of polypeptides of SED ID NO: 34 would retain the desired activity, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the absence of working examples directed to variants and the breath of claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, first paragraph – Written Description, maintained.

7. Claims 4-5 and 12-13 remain rejected along with the previously presented claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for reasons set forth in the previous Office Actions pages 9-12 of 28, June 2004, pages 17-19 of 31, March 2005 and pages 15-17 of 29, August 2005. Briefly, the Applicants were not in possession of all or a significant number of polypeptides that have 95-99% homology to SED ID NO: 34 or fragments recited and still retain the function of SED ID NO: 34.

Applicants discuss the legal standards applied when evaluating Written Description, including the requirement that written description depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure (page 33, 23 November 2005). The examiner takes no issue with the discussion of general requirements for evaluating Written Description in this case. Applicants argue that they are in possession of the invention as of the effective filing date. Applicants assert that the inventor is not required to describe every single detail of his/her invention. With respect to Applicants specific argument that given the skill in the art, specifying highly stringent condition leads to "no substantial variation within the [claimed] genus" and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. These

arguments have been previously addressed in the Office Action dated 29/8/05. Applicants' arguments have been fully considered but are not found to be persuasive.

However, Applicants have not described or shown possession of all polypeptides 95-99% homologous to SED ID NO: 34 or the various fragments, that still retain the function of SED ID NO: 34. Furthermore Applicants have not described a representative number of species that have 95-99% homology to SED ID NO: 34 or fragments of SED ID NO: 34, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SED ID NO: 34.

As discussed in the previous Office Action (29 August 2005) even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1277 polypeptides, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The claimed product itself is required. Recitation of the phrase "wherein the polypeptide is more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts respectively, or wherein the said isolated polypeptide is encoded by a polynucleotide that is more highly normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor counterparts or fragments thereof used to generate an antibody that specifically binds SEQ ID NO: 34," (amended claims, 7 April 2005), is not adequate to describe polynucleotides encoding the PRO1277 polypeptides that have 95-99% homology to the PRO1277 polypeptide, since there was no reduction to practice to support the amended claims.

Specifically, there is no way of knowing which, if any variants would have the same property of over-expression in the specific tissues. There is no nexus between the degree of homology and regulation of gene expression. Until one identifies a particular variant that is over-expressed or not, one of skilled in the art would not know the expression profile of the variant. The mere sequence alone will not allow one of skilled in the art to predict expression. Applicants made no variant polypeptides, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

At pages 34-35 of the Brief, Appllicant cites the Written Description Guidelines of the U.S. Patent Office and argues that in Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for claimed catalytic activity. Thus, it is asserted that written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the Applicants had not made any variants. Appllicants contend that similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO: 34 in skin or esophageal tissue samples. The fact pattern in the instant application is not analogous to Example 14 in the Revised Interim Written Description Guidelines. In Example 14 of the Guidelines, the claimed protein variants have a high percent sequence identity in

combination with a specific functional limitation. In the example, the protein catalyzes the reaction of A→B and thus, methods of generating variants of the protein that have 95% identity and retain its activity are conventional in the art because deletions, substitutions, insertions, and additions of uncritical amino acid residues would not affect the enzyme activity. Moreover, such an enzyme would have a conserved structure that is responsible for the enzyme activity. Thus, it is likely predictable, based upon percent identity, which variant would share the same function. In contrast, in the instant case, polypeptide of PRO1277 has no utility and has no disclosed function. Furthermore, the specification and the claims do not disclose the identification of any particular portion of the PRO1277 structure that must be conserved in order to conserve the required function.

Applicants also assert that by citing *In re Wallach* argue that the Examiner's premise that a large genus can not be adequately described a single species is simply wrong (see bottom of page 37-38). However, the fact pattern present in *In re Wallach* is different from instant invention. The claims were directed to polynucleotides sequences encoding the polypeptide. However, the court affirmed the Board's determination (USPTO position) that the specification of the patent application did not provide an adequate written description of the pending claims. Applicants as in the instant application did not provide any evidence that there is any known or disclosed correlation between the combination of a partial structure of a protein and the protein's biological activity.

8. No Claims are allowed.

9. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action

Contact information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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